Malignant optic glioma - the spectrum of disease in a case series

Traber, G L ; Pangalu, A ; Neumann, M ; Costa, J ; Weller, M ; Huna-Baron, R ; Landau, K

Abstract: PURPOSE Malignant optic glioma of adulthood is a rare, invasive neoplasm of the anterior visual pathway with 66 cases reported in the literature. It presents as anaplastic astrocytoma (WHO grade III) or glioblastoma (WHO grade IV). The present case series covers the spectrum of disease manifestations, discusses neuroradiological findings, and reviews the current literature. METHODS Retrospective case series of five patients from three tertiary referral centers and literature review. RESULTS Visual loss with or without pain was the presenting symptom in all patients (two women, three men). Two patients were initially misdiagnosed as optic neuritis, and one patient as atypical non-arteritic anterior ischemic optic neuropathy (NAION). A neoplastic disease was suspected in the two remaining patients. MRI features were iso- to hypointensity on T1-weighted native images, contrast enhancement, and hyperintensity on T2-weighted images. Biopsy was generally diagnostic; however, one patient required two biopsies for diagnosis. The series includes an exceptional case of intraocular tumor extension and vitreous spread. The disease was lethal within one to two years in all patients. CONCLUSIONS Malignant optic glioma is a diagnostic challenge and remains a devastating and lethal disease. Advances in the understanding of tumor biology have yet failed to translate into effective treatment regimens.

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	Malignant optic glioma is a diagnostic challenge and remains a devastating and lethal disease. Advances in the understanding of tumor biology have yet failed to translate into effective treatment regimens.

Cover Letter
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Zurich, April 2015

Submission of Manuscript

Dear Editor,

Please find enclosed our *revised* manuscript entitled

Malignant optic glioma – the spectrum of disease in a case series

Ghislaine L Traber, MD[1A], Athina Pangalu, MD[1B], Manuela Neumann, MD[1C, 2], Joao Costa, MD[3], Michael Weller, MD[1D], Ruth Huna-Baron, MD[4], Klara Landau, MD[1A]

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which we would like to submit for publication to 'Graefe's Archive for Clinical and Experimental Ophthalmology'.

The thorough review of our manuscript was much appreciated. We have addressed the issues raised and suggestions made by the reviewers.

We hope that you will find our manuscript suitable for publication in 'Graefe's Archive for Clinical and Experimental Ophthalmology'.

Kind regards,

Ghislaine Traber

Response to referees' comments

The thorough review of our manuscript was much appreciated. We have addressed the issues raised and suggestions made by the reviewers.

Reviewer comments:

Reviewer #1: The authors report on 5 patients with malignant optic gliomas. The text is concise and very informative with excellent illustrations. For the sake of completeness the authors may wish to add some minor data to the text.

COMMENT
1. A simplified table showing the current WHO classification of CNS astrocytic tumors. This would give the distant reader an overview of the spectrum of the tumors so that the contribution of this study can be better appreciated.
RESPONSE:
Table 1 gives an overview on the current WHO classification of CNS astrocytic tumors.

COMMENT
2. Except for patient 4, the site of biopsies and how they were taken are not clear.
RESPONSE:
This information has been added to the case descriptions in the results section.

Reviewer #2: Dear Author,

Your article on malignant optic glioma is of high scientific interest .It supposes , death beeing oftently occuring quite quickly , that the disease can be sometimes misdiagnosed in some parts of the world.The absence of effective treatment is compensating this unfortunate type of situation , however at this time of our scientific knowledges .

Your article is well written but I wish to make some comments to improve your work and increase its impact when it will be read by others .

COMMENT
1.The paragraph Methods should be increased in density and comprise the description of the geographic origin of the patients .You are speaking about three referral centers and reading the authors names can induce in this knowledge but it has to be precised in this paragraph .
RESPONSE:
Information about the referral centers has been added in this paragraph. (p. 4)

COMMENT
Also , the ages and sex of the patients should be mentioned here .
RESPONSE:

We have now indicated gender and age in the revised Table 2.

COMMENT
Subjective functional signs described by the patients and suspected diagnosis should also be writte here, even if they are repeated in the table.
RESPONSE:
Subjective signs were again described in the results paragraph and in Table 2.

COMMENT
Did the patients have other ophthalmological examinations than Fundus examination (whith which type ? Biomicroscopy or/and indirect ophthalmoscopy ?)such as fluorescein angiography for example ?
RESPONSE:
This information has been added to the methods paragraph (p. 4-5)

COMMENT
Moreover always in this paragraph, if all patients have had radiotherapy and chemotherapy , the field of irradiation for radiotherapy and
the doses for both technics should be precised .It should be interesting to know if there were differences in these technics according to the 3 centers .
RESPONSE:
The authors felt that discussion of radiotherapy and chemotherapy belongs to the result section and discussion sections rather than to the methods section.
More precise information about radiotherapy and chemotherapy was given for each individual case (results, p. 5-8, see also revised Table 2). This topic is also addressed in the discussion section. (p. 11)

COMMENT
And the same remark for biopsy .A short description of the way of orbital bone trepanation should be given.Was it always lateral orbitotomy ? When or why could pterional craniotomy be choosen ?
RESPONSE:
Indication for lateral orbitotomy or pterional craniotomy is now described in the introduction p.4. Description of the surgical approach has been published elsewhere (Winn HR. Youmans Neurological Surgery, 6th ed. Philadelphia: Elsevier Saunders 2011) and is felt to be beyond the scope of this paper.

COMMENT
Also it should be mentioned why you do not produce imaging details for patients 2 and 5 .
RESPONSE:
Imaging is available for all five patients. The most illustrative cases were chosen for publication.

COMMENT
2.The paragraph Results is well presented.If it is better introduced by the paragrah Methods, it will be easier to be read .
RESPONSE
We improved the Method section accordingly.

COMMENT

3.The paragraph on Discussion should include a table on all the literature results .Even if it is more simple than yours and do not precise all details of the 45+16 patients , duration of survival , suspected diagnosis, ages, sex, therapy for instance could be mentioned and really give to the paper another dimension .

RESPONSE:

Table 3 summarizes the findings of those 16 patients published since Wabbels et al. Wabbels et al themselves published a table summarizing the previous 45 cases.

COMMENT

Is CT Scan of any complementary interest in this optic nerve cancer ?

RESPONSE:

CT imaging is not helpful in diagnosing malignant optic glioma. (added to discussion p. 10)

COMMENT

Also in the discussion , you should explain if the modalities of irradiation have been changed with the time and the center, and the same for chemotherapy dosis .Why is the molecule TEMOZOLOMIDE choosen ? One has to know better which small progresses have been done in the early diagnosis , in imaging, in choices of chemotherapies, in modalities of irradiation.

RESPONSE:

These questions have been addressed in the Discussion section – see page 11.

Wishing you a rapid publication with some complements of information !

Title Page

Malignant optic glioma – the spectrum of disease in a case series

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ABSTRACT

Purpose

Malignant optic glioma of adulthood is a rare, invasive neoplasm of the anterior visual pathway with 66 cases reported in the literature. It presents as anaplastic astrocytoma (WHO grade III) or glioblastoma (WHO grade IV). The present case series covers the spectrum of disease manifestations, discusses neuroradiologic findings and reviews the current literature.

Methods

Retrospective case series of five patients from three tertiary referral centers and literature review.

Results

Visual loss with or without pain was the presenting symptom in all patients (two women, three men). Two patients were initially misdiagnosed as optic neuritis, and one patient as atypical non-arteritic anterior ischemic optic neuropathy (NAION). A neoplastic disease was suspected in the two remaining patients. MRI features were iso- to hypointensity on T1-weighted native images, contrast enhancement, and hyperintensity on T2-weighted images. Biopsy was generally diagnostic, however, one patient required two biopsies for diagnosis. The series includes an exceptional case of intraocular tumor extension and vitreous spread. The disease was lethal within one to two years in all patients.

Conclusions

Malignant optic glioma is a diagnostic challenge and remains a devastating and lethal disease. Advances in the understanding of tumor biology have yet failed to translate into effective treatment regimens.

Keywords

Malignant optic glioma, glioblastoma, anaplastic astrocytoma, MRI, intraocular tumor extension.

INTRODUCTION

Malignant optic glioma of adulthood is a rare entity first defined and reviewed by Hoyt et al. in 1973 {Hoyt et al., 1973, Brain, 96, 121-32}. The tumor arises in the optic nerve, chiasm or tract, and may present as a multifocal neoplasm. It is a high-grade astrocytoma, as such either an anaplastic astrocytoma (WHO grade III) or a glioblastoma (WHO grade IV) {Louis et al., 2007, IARC, Lyon.}. In addition to mitotic activity defining high-grade astrocytomas, the presence of necrosis or vascular proliferation is required for grade IV diagnosis. Table 1 gives an overview of the current WHO classification of CNS astrocytic tumors. Patients with malignant optic glioma usually suffer bilateral visual loss within a few weeks and die within one to two years. Upon initial presentation patients are frequently misdiagnosed with optic neuritis, anterior ischemic optic neuropathy or primary retinal vascular occlusion. Intraocular signs range from a normal fundus to disc edema, disc pallor and retinal vascular occlusions. Intraocular growth of tumor is rare. Biopsies need to be obtained to confirm diagnosis. Lateral orbitotomy is performed for tumors affecting the orbital part of the optic nerve, whereas tumors with intracerebral extension are best accessed by pterional craniotomy {Winn, Youmans Neurological Surgery, 6th ed. Philadelphia: Elsevier Saunders 2011.}.

The present case series covers the spectrum of disease manifestations including one exceptional case of intraocular tumor manifestation, and allows discussion of neuroradiologic findings.

METHODS

Retrospective case series of five patients from three tertiary referral centers (1997 – 2011) and literature review. Three patients from the Zurich University Hospital, Switzerland, one patient from the Goldschleger Eye Institute Tel Aviv, Israel, and one

patient from the Egas Moniz Hospital Lisbon, Portugal are reported. All patients underwent biomicroscopy of the fundus and imaging of brain and orbits. In two patients fluorescein angiography, and in one patient more extensive work-up with an electroretinogram, genetic testing, and temporal artery biopsy was performed. Diagnosis was confirmed by biopsy in all patients. No ethical board approval was required from our institute when the data was collected (2012-2013).

RESULTS

Three men and two women aged 54 to 76 years (mean 66.8 years) with malignant optic glioma were identified. Table 2 summarizes their disease manifestation and disease progression.

Patient 1 presented with left-sided visual loss to hand movement (HM) level for five weeks. On examination, the patient had a left relative afferent pupillary defect (RAPD), a blurred left disc margin, pain on retropulsion, and a junctional scotoma. Fluorescein angiography showed unspecific late leakage of the left disc. These findings suggested a retrobulbar and prechiasmatic lesion. MRI showed involvement of the left optic nerve, optic chiasm, thalamus, mesencephalon and pons with enhancement on T1-weighted images, and hyperintensity on FLAIR and T2 images (Fig. 1). There was progression to disc edema with stasis retinopathy seven weeks later, and to optic atrophy another three months later. The right fundus was normal. Histopathology was obtained from a biopsy via left pterional craniotomy and revealed glioblastoma. The patient received combined temozolomide chemoradiotherapy with irradiation of the involved field (30 x 2 Gy planned, 24 x 2 Gy given), however, died during therapy four and a half months after diagnosis, probably due to tumorous infiltration of the brainstem.

Patient 2 presented with painful eye movements, scintillations, right-sided visual loss (20/30), right RAPD and disc edema. The clinical picture and MRI scan with right optic nerve swelling, enhancement on T1-weighted images and hyperintensity in T2-weighted images were interpreted as optic neuritis. The patient was placed on intravenous methylprednisolone and oral taper twice with resolution of pain, but had progressive visual loss to hand movements (HM) within two months due to a central scotoma in the right eye. The initial MRI scan had revealed a 2 cm lesion with abnormal signal intensity and a 2 mm enhancing spot in the right medial temporal gyrus of unknown etiology. Four months later, follow-up MRI showed progression of the latter. The subsequent cerebral biopsy allowed diagnosis of a multifocal glioblastoma. Despite combined temozolomide chemoradiotherapy with irradiation of the involved field (30 x 1.8 Gy), and bevacizumab salvage therapy, the patient experienced progressive tumor growth with bilateral involvement of the optic nerves, chiasm, tracts, as well as left thalamus und right temporal lobe. After seven months, vision in the left eye started to deteriorate, finally resulting in bilateral optic disc atrophy with no light perception (NLP) of the right eye and faint light perception (LP) of the left eye. The patient died within 18 months of disease onset.

Patient 3 reported painless right-sided visual loss over night. Initial visual acuity of right eye HM and left eye 20/30 further deteriorated to right eye NLP and left eye 20/400 with temporal hemianopia within six weeks. Fundoscopy showed a membranous structure of the right optic disc (Fig. 2a) with progressive vitreous spread over a four months period (Fig. 2b-c). MRI demonstrated a homogeneously enhancing chiasmatic tumor (Fig. 2d) with extension to both optic tracts and optic nerves (right intraorbital and left intracranial portion). The tumor was hyperintense on

T2-weighted images, and isointense on native T1 images. Biopsy via right pterional craniotomy allowed the diagnosis of anaplastic astrocytoma. The tumor progressed despite involved-field radiotherapy (34 x 1.8 Gy). The patient became comatose and died from pneumonia six months after diagnosis. Autopsy finally revealed pleomorphic, astrocytic tumor cells, pseudopalisading necrosis and microvascular proliferation (Fig. 2e-f), consistent with the diagnosis of glioblastoma.

Patient 4 presented with painless unilateral visual blur (right 20/50, left 20/25), impaired color vision and RAPD in the right eye. Both fundi were normal. Automated perimetry revealed superior constriction on the right and an inferior arcuate defect on the left. MRI was read as suspected vague enhancement of the right optic nerve. Lumbar puncture and laboratory work-up for inflammatory or hematological diseases were normal. Intravenous methylprednisolone for five days and oral taper was initiated without effect. Vision deteriorated to NLP in both eyes within six weeks. At that point an electroretinogram was obtained in order to rule out carcinoma associated retinopathy. Genetic testing for Leber hereditary optic neuropathy was negative, temporal artery biopsy ruled out arteritis, and fluorescein angiography was normal. A follow-up MRI three months after onset of symptoms showed bilateral optic nerve enhancement on T1-weighted images, and hyperintensity in T2-weighted images. Optic nerve biopsy via lateral orbitotomy was unrevealing. MRI two months later showed progressive enlargement of the prechiasmatic optic nerves and chiasm suggestive for malignant optic glioma. Biopsy via pterional craniotomy confirmed glioblastoma. Combined temozolomide chemoradiotherapy was recommended. However, the patient decided against temozolomide. The tumor progressed despite involved-field irradiation (28 x 1.8 Gy) and the patient died one year after presentation.

Patient 5 noticed painless visual loss in the right eye for five weeks. Visual acuity was 20/100 with impaired color vision and RAPD in the right eye, and 20/30 with normal color vision in the left eye. Fundoscopy revealed optic disc swelling with hemorrhages and exsudates in the right eye. An arteritic cause could be ruled out, and a diagnosis of atypical NAION was made. Four months later, the patient was referred with progressive deterioration to LP in the right eye and visual loss in the left eye to finger counting level. Fundoscopy revealed shunt vessels and a combined retinal artery and venous occlusion in the right eye, whereas the left fundus was normal. Visual fields were not tested because vision was too low. The MRI was suggestive for malignant optic glioma with bilateral thickening and enhancement of the prechiasmatic optic nerves, chiasm, and tract on T1-weighted images, T1 iso- to hypointensity on native images, and hyperintensity on T2-weighted images (Fig. 3a-c). The diagnosis of glioblastoma was confirmed by right optic nerve biopsy via pterional craniotomy. The patient underwent involved-field radiotherapy, however, died within seven months of symptom onset. Precise information about radiotherapy dose could not be retrieved from the records.

DISCUSSION

Malignant optic glioma of adulthood is a rare, invasive neoplasm of the anterior visual pathway with 66 cases reported. By 2004, Wabbels et al. {Wabbels et al., 2004, Graefes Arch Clin Exp Ophthalmol, 242, 741-8} reviewed 45 cases. Including our five patients, 21 additional cases have been published since (Tables 2 and 3) {Hahn et al., 2004, Rofo, 176, 1700-1}{Danesh-Meyer et al., 2005, Arch Ophthalmol, 123, 694-700}{Hartel et al., 2006, W V Med J, 102, 29-31}{Dinh et al., 2007, J Clin Neurosci, 14, 502-5}{Romano et al., 2007, Neurologia, 22, 389-90}{Abou-Zeid et al., 2008, Br J Neurosurg, 22, 772-3}{Chacko et al., 2010, Br J Ophthalmol, 94, 782-3, 812}{Dumas-Stoeckel et al., 2010, J Fr Ophtalmol, 33, 564-7}{Matloob et al., 2011, J Clin Neurosci}{Simao et al., 2011, Surv Ophthalmol, 56, 362-70}{Lincoff et al., 2012, J Neuroophthalmol, 32, 82-5}{Kang et al., 2012, Neuroophthalmology, 36, 59-63}{Ashur-Fabian et al., 2013, Anticancer Drugs, 24, 315-23}{Colpak et al., 2014, Surv Ophthalmol}. Mean age of onset of all 66 cases is 57 years (standard deviation ±15; range 22 – 83), with women and men almost equally affected (30 females and 36 males). It rarely occurs in paediatric populations, either as a primary high-grade glioma {Cirak et al., 2000, Acta Radiol, 41, 375-6}{Wong et al., 1987, Cancer, 60, 1847-55}{Safneck et al., 1992, Can J Neurol Sci, 19, 498-503}{Brooks et al., 1976, Clin Pediatr (Phila), 15, 557-61} or as malignant transformation of low-grade gliomas {Wilson et al., 1976, Neurology, 26, 322-5}{Wong et al., 1987, Cancer, 60, 1847-55}{de Keizer et al., 1989, Am J Ophthalmol, 108, 717-25}{Zoeller et al., 2010, J Neurosurg Pediatr, 5, 507-10}.

Patients suffer from rapidly progressive visual acuity and visual field loss, usually leading to blindness. Depending on tumor localization and extension, visual field defects might be unspecific or show localizing patterns.

With onset of symptoms, all our patients experienced visual loss within one to two months in at least one eye. Patient 2 had a delayed involvement of the fellow eye after seven months. Patient 1 initially seemed to have a strictly unilateral infiltration of the chiasm (Fig. 1) with preserved visual function of the fellow eye. However, there was neuroradiologic evidence of diffuse chiasmatic infiltration and extension to both optic tracts within four months of disease onset, two weeks before the patient passed away. Interestingly, purely unilateral involvement of the anterior visual pathway has been reported in one patient described by Wabbels et al. {Wabbels et al., 2004, Graefes Arch Clin Exp Ophthalmol, 242, 741-8} with a follow-up period of 12 months until death.

At an early stage, clinical findings might suggest anterior ischemic optic neuropathy (patient 5) or inflammatory neuropathy (patient 2 and 4) with minimal neuroradiologic findings and transient responsiveness to steroids. However, progressive visual acuity and visual field deterioration, progressive dyschromatopsia, subsequent retinal vasular occlusions (patient 1), ocular ischemia as well as ocular pain, headaches, ophthalmoplegia, proptosis and other neurological deficits depending on tumor localization and extension {Wabbels et al., 2004, Graefes Arch Clin Exp Ophthalmol, 242, 741-8} point towards a possible malignant infiltrative disease, and a follow-up MRI should be obtained.

Neuroradiologic findings are unspecific, usually described as contrast enhancement and eventual thickening of the optic nerve, chiasm or tract in T1-weighted images {Miller, 2004, Eye (Lond), 18, 1026-37}{Wabbels et al., 2004, Graefes Arch Clin Exp Ophthalmol, 242, 741-8}, with iso- to hypointensity on native T1 images {Chong, 2006, Cancer Imaging, 6, S27-31}{Friedman and Hollander, 1998, Radiographics, 18, 1046-8}. T2 *hyper*intensity of the affected anterior visual pathway is a matter of debate {Chong, 2006, Cancer Imaging, 6, S27-31}. It was first described by Albers et

al. {Albers et al., 1988, Neurology, 38, 1071-4} in one patient. Friedman et al. {Friedman and Hollander, 1998, Radiographics, 18, 1046-8} presented a second case, and suggested T2 hyperintensity as a possible distinguishing feature of malignant optic glioma versus sarcoidosis with its tendency to *hypo*intensity on T2-weighted images. However, T2 signal intensity is variable in sarcoidosis {Becker et al., 2010, Eur J Radiol, 74, 299-313}. Most authors did not comment on neuroradiologic findings of T2-weighted images in malignant optic glioma. In two more recent cases {Hahn et al., 2004, Rofo, 176, 1700-1}{Lincoff et al., 2012, J Neuroophthalmol, 32, 82-5} T2 hyperintensity was described, whereas Wabbels et al. {Wabbels et al., 2004, Graefes Arch Clin Exp Ophthalmol, 242, 741-8} explicitly did not find T2 hyperintensity of the optic nerve and chiasm. Our case series supports T2 or FLAIR hyperintensity as a characteristic, albeit unspecific finding of malignant optic glioma, since it was evident in all five patients. This is consistent with neuroradiologic findings in the better characterized cerebral high-grade gliomas {Clarke and Chang, 2012, Cancer J, 18, 26-31}. With regard to imaging features, differential diagnosis of a suspected malignant optic glioma still includes demyelinating, infectious, granulomatous, vasculitic and infiltrative optic neuropathies {Becker et al., 2010, Eur J Radiol, 74, 299-313}. CT imaging is not helpful in diagnosing malignant optic glioma.

So far, obtaining a biopsy is mandatory for diagnosis, and in case of an unspecific inflammatory histopathologic result, the biopsy might have to be repeated in a patient with a progressive, presumably neoplastic disease as in our patient 4 {Matloob et al., 2011, J Clin Neurosci}. Interestingly, patient 3 had documented progression of a grade III glioma (biopsy) to a grade IV glioma (autopsy), which is unique in the current literature on adult malignant optic glioma. However, it might also simply reflect the tumor heterogeneity with sampling bias.

Considering the aggressively invasive behavior of malignant astrocytomas, intraocular tumor extension is surprisingly rare. While a mechanical barrier at the level of the lamina cribrosa seems plausible, a biological barrier influencing local tumor growth might be suspected as well. Intravitreal seeding of malignant optic glioma of adulthood has not been reported before and makes our case 3 unique. Dumas-Stoeckel et al. {Dumas-Stoeckel et al., 2010, J Fr Ophtalmol, 33, 564-7} presented one patient in the French literature with subretinal tumor extension and combined central retinal vein and artery occlusion. Neither in this latter nor in our patient was intraocular growth confirmed histologically, though.

The standard of care for newly diagnosed high-grade astrocytomas consists of surgery or biopsy as feasible followed by radiotherapy alone (WHO grade III) or temozolomide chemoradiotherapy (WHO grade IV). The introduction of temozolomide increased the median survival of glioblastoma patients by 2-3 months and the likelihood of 2-year survival from 10% to 26% {Stupp et al., 2005, N Engl J Med, 352, 987-96}. In contrast, the standard radiotherapy regimen of 54-60 Gy administered in 1.8-2 Gy fractions has remained essentially unaltered over the last decades. Risk structures such as optic nerves, chiasm or brain stem commonly receive no more than 54 Gy. Recurrence or progression may be treated with re-resection, a second course of radiotherapy, or most commonly, using systemic alkylating agent chemotherapy or the VEGF antibody, bevacizumab {Weller et al., 2014, Lancet Oncol, 15, e395-403}. The course of disease has not considerably improved over the last century {Hoyt et al., 1973, Brain, 96, 121-32}, and malignant optic glioma remains lethal within one to two years {Wabbels et al., 2004, Graefes Arch Clin Exp Ophthalmol, 242, 741-8}. The latter also holds true for our patients. Advances in the understanding of tumor biology have yet failed to translate into effective treatment regimens {Weller et al., 2012, Cancer J, 18, 40-4}. However as

research evolves, it is our hope that patients affected from a disease as devastating as malignant optic glioma will benefit from early diagnosis and treatment in the future.

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Legends:

Fig. 1: Coronal T2-weighted images of patient 1 with multifocal glioblastoma show hyperintensity of the left optic nerve (a), left chiasm (b) and infiltration of thalamus, mesencephalon and pons (c). Four months later the tumor diffusely infiltrated the whole chiasm.

Fig. 2 (patient 3): A membranous structure of the right optic disc (a) progressed in size (b) and resulted in vitreous spread (c) over a four months period. The left optic nerve was unremarkable. The axial (d) MRI scan shows impressive thickening of the chiasm with homogeneous contrast enhancement on T1-weighted images. Autopsy revealed diffuse infiltration of the optic nerve and chiasm with pleomorphic, astrocytic tumor cells, with pseudopalisading necrosis (e) and microvascular proliferation (f), the two features distinguishing glioblastoma from anaplastic astrocytoma.

Fig. 3 (patient 5): The coronal MRI scans show bilateral thickening of the optic nerve with hyperintensity in T2-weighted images (a), iso- to hypointensity in native T1-weighted images (b) and bilateral enhancement (c) five months after onset of symptoms.

Table 1: Current WHO classification of CNS astrocytic tumors, modified from Louis et al. (2007) {Louis et al., 2007, IARC, Lyon.}

Table 2: Summary of patient characteristics, disease manifestation and disease progression

Abbreviations: OD right eye, OS left eye, OU both eyes, VL visual loss, AA anaplastic astrocytoma WHO grade III, GBM glioblastoma WHO grade IV, w weeks, mt months, TMZ/RT → TMZ radiotherapy with concomitant and adjuvant temozolomide (according to Stupp et al. 2005) {Stupp et al., 2005, N Engl J Med, 352, 987-96}, RT radiotherapy, TMZ temozolomide, NAION non-arteritic ischemic optic neuropathy, CAR carcinoma associated retinopathy, CRAO central retinal artery occlusion, CRVO central retinal vein occlusion, ↓ hypointense, → isointense, ↑ hyperintense, +contrast ↑ contrast-enhancing.

Table 3: Summary of 16 published cases since the review of 45 cases by Wabbels et al. (2004) {Wabbels et al., 2004, Graefes Arch Clin Exp Ophthalmol, 242, 741-8}. A case of gemistocytic astrocytoma was included because it had a rather malignant course with survival of 12 months despite multimodality treatment (Simao et al. 2011).

Abbreviations: NK not known, OD right eye, OS left eye, OU both eyes, AA anaplastic astrocytoma WHO grade III, GBM glioblastoma WHO grade IV, w weeks, mt months, chemo chemotherapy (chemotherapeutic agent indicated where available), RT radiotherapy (total dose indicated where available), chemo/RT combined chemoradiotherapy, TMZ temozolomide, PION posterior ischemic optic

neuropathy, NAION non-arteritic anterior ischemic optic neuropathy, CRAO central retinal artery occlusion, CRVO central retinal vein occlusion

Malignant optic glioma

Astrocytic tumors	WHO grade I	WHO grade II	WHO grade III	WHO grade IV
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•

Table 1: Current WHO classification of CNS astrocytic tumors, modified from Louis et al. (2007) {Louis et al., 2007, IARC, Lyon.}

Malignant optic glioma

Patient	Sex/Age	Pain	Suspected Diagnosis	Fundus	Visual Fields	MRI	Time to Blindness	WHO grade	Therapy	Time to Death	Comments
1	M, 65	On retro-pulsion	Tumor	Disc edema OS → stasis retinopathy → disc atrophy Normal OD	VL OS with junctional scotoma OD	T1+contrast ↑ T2↑ / FLAIR↑	5 w (OS) OD unknown	IV, GBM	TMZ/RT → TMZ (24 x 2 Gy given, 30 x 2 Gy planned)	4.5 mt	- Multifocal GBM
2	M, 54	Yes	Optic neuritis	Disc edema OD → disc atrophy OU	Central scotoma OD	T1+contrast ↑ T2↑	2 mt (OD) 7 mt (OS)	IV, GBM	TMZ/RT → TMZ (30 x 1.8 Gy), Bevacizumab at progression	18 mt	- Multifocal GBM
3	F, 64	No	Tumor	Disc membrane OD → vitreous spread Initially normal OS	VL OD with temporal hemianopia OS	T1→ T1+contrast ↑ T2↑	<1 w (OD) 6 w (OS)	III, AA → IV, GBM	RT (34 x 1.8 Gy)	6 mt	- Intraocular tumor growth - III, AA (biopsy) → IV, GBM (autopsy)
4	M, 75	No	Optic neuritis, CAR	Initially normal OU	OD unspecific OS arcuate scotoma	T1+contrast ↑ T2↑	6 w (OU)	IV, GBM	RT (28 x 1.8 Gy), patient decided against TMZ	12 mt	- Only second biopsy diagnos
5	F, 76	No	NAION	Disc edema → stasis retinopathy, exsudates → CRAO & CRVO OD Initially normal OS	Not documented.	T1↓→ T1+contrast ↑ T2↑	5 w (OD) 4 mt (OS)	IV, GBM	RT (dose not known)	7 mt	- Retinal vessel occlusion

Table 2: Summary of patient characteristics, disease manifestation and disease progression
Abbreviations: OD right eye, OS left eye, OU both eyes, VL visual loss, AA anaplastic astrocytoma WHO grade III, GBM glioblastoma WHO grade IV, w weeks, mt months, TMZ/RT → TMZ radiotherapy with concomitant and adjuvant temozolomide according to Stupp et al. (2005) {Stupp et al., 2005, N Engl J Med, 352, 987-96}, RT radiotherapy, TMZ temozolomide, NAION non-arteritic anterior ischemic optic neuropathy, CAR carcinoma associated retinopathy, CRAO central retinal artery occlusion, CRVO central retinal vein occlusion, ↓ hypointense, → isointense, ↑ hyperintense, +contrast ↑ contrast-enhancing

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Malignant optic glioma

Author and year	Sex/Age	Eye	Time to blindness	Presumed diagnosis	Histology AA/GBM	Therapy	Time to death
Hahn et al. 2004	M/53	OS	NK	neurosarcoidosis	GBM	chemo (nimustin, teniposid) and RT	NK
Danesh-Meyer et al. 2005	F/77	OU	2 mt OD NK OS	arteritic PION	NK (biopsy done)	chemo and RT (60 Gy)	11 mt
	M/60	OU	NK	inflammatory or infiltrative optic neuropathy	AA	RT (52 + 15 + 12.5 Gy)	20 mt
	F/77	OU	18mt OD NK OS	NAION	AA	RT (50.4 Gy)	30 mt
Hartel et al. 2006	M/59	OU	<1 mt OD NK OS	NK	GBM	--	8 w
Dinh et al. 2007	F/48	OU	NK	Optic nerve tumor	GBM	RT (54 Gy)	14 mt
Romano et al. 2007	F/69	OU	4 mt OU	NAION	AA	NK	NK
Abou-Zeid et al. 2008	M/56	OU	<1 mt OU	metastatic brain disease from renal primary	GBM	RT	3 mt
Chacko et al. 2010	M/48	OU	1 mt OD NK OS	optic neuritis	AA	chemo and RT	11 mt
Dumas-Stoeckel et al. 2010	M/73	OU	<1 mt OS 4 mt OD	NAION	AA	chemo/RT	~5-6 mt
Matloob et al. 2011	F/63	OU	<1 mt OD ~3-6 mt OS	optic neuritis	GBM	chemo (TMZ)	6 mt
Simao et al. 2011	M/62	OU	3 mt OD NK OS	optic nerve tumor	Diffuse astrocytoma (gemistocytic)	chemo and RT	12 mt
Lincoff et al. 2012	M/83	OS	<1 mt OS NK OD	large differential for combined CRAO/CRVO	GBM	NK	NK
Kang et al. 2012	F/60	OU	2 mt OU	inflammatory optic neuropathy	AA or GBM (small sample)	TMZ/RT (60 Gy) → TMZ	8 mt
Ashur-Fabian et al. 2013	M/64	OU	~6 mt OS NK OD	NK	GBM	TMZ/RT (60 Gy) → TMZ, propylthiouracil, carboplatin	54 mt
Colpak et al. 2014	M/47	OU	<1 mt OS NK OD	inflammatory or infiltrative optic neuropathy	GBM	--	3 mt

Table 3: Summary of 16 published cases since the review of 45 cases by Wabbels et al. (2004) (Wabbels et al., 2004, Graefes Arch Clin Exp Ophthalmol, 242, 741-8). A case of gemistocytic astrocytoma was included because it had a rather malignant course with survival of 12 months despite multimodality treatment (Simao et al. 2011)
Abbreviations: NK not known, OD right eye, OS left eye, OU both eyes, AA anaplastic astrocytoma WHO grade III, GBM glioblastoma WHO grade IV, w weeks, mt months, chemo chemotherapy (chemotherapeutic agent indicated where available), RT radiotherapy (total dose indicated where available), chemo/RT combined chemoradiotherapy, TMZ temozolomide, PION posterior ischemic optic neuropathy, NAION non-arteritic anterior ischemic optic neuropathy, CRAO central retinal artery occlusion, CRVO central retinal vein occlusion

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Malignant optic glioma

Title Page

Malignant optic glioma – the spectrum of disease in a case series

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ABSTRACT

Purpose

Malignant optic glioma of adulthood is a rare, invasive neoplasm of the anterior visual pathway with 66 cases reported in the literature. It presents as anaplastic astrocytoma (WHO grade III) or glioblastoma (WHO grade IV). The present case series covers the spectrum of disease manifestations, discusses neuroradiologic findings and reviews the current literature.

Methods

Retrospective case series of five patients from three tertiary referral centers and literature review.

Results

Visual loss with or without pain was the presenting symptom in all patients (two women, three men). Two patients were initially misdiagnosed as optic neuritis, and one patient as atypical non-arteritic anterior ischemic optic neuropathy (NAION). A neoplastic disease was suspected in the two remaining patients. MRI features were iso- to hypointensity on T1-weighted native images, contrast enhancement, and hyperintensity on T2-weighted images. Biopsy was generally diagnostic, however, one patient required two biopsies for diagnosis. The series includes an exceptional case of intraocular tumor extension and vitreous spread. The disease was lethal within one to two years in all patients.

Conclusions

Malignant optic glioma is a diagnostic challenge and remains a devastating and lethal disease. Advances in the understanding of tumor biology have yet failed to translate into effective treatment regimens.

Keywords

Malignant optic glioma, glioblastoma, anaplastic astrocytoma, MRI, intraocular tumor extension.

INTRODUCTION

Malignant optic glioma of adulthood is a rare entity first defined and reviewed by Hoyt et al. in 1973 [1]. The tumor arises in the optic nerve, chiasm or tract, and may present as a multifocal neoplasm. It is a high-grade astrocytoma, as such either an anaplastic astrocytoma (WHO grade III) or a glioblastoma (WHO grade IV) [2]. In addition to mitotic activity defining high-grade astrocytomas, the presence of necrosis or vascular proliferation is required for grade IV diagnosis. Table 1 gives an overview of the current WHO classification of CNS astrocytic tumors. Patients with malignant optic glioma usually suffer bilateral visual loss within a few weeks and die within one to two years. Upon initial presentation patients are frequently misdiagnosed with optic neuritis, anterior ischemic optic neuropathy or primary retinal vascular occlusion. Intraocular signs range from a normal fundus to disc edema, disc pallor and retinal vascular occlusions. Intraocular growth of tumor is rare. Biopsies need to be obtained to confirm diagnosis. Lateral orbitotomy is performed for tumors affecting the orbital part of the optic nerve, whereas tumors with intracerebral extension are best accessed by pterional craniotomy [3].

The present case series covers the spectrum of disease manifestations including one exceptional case of intraocular tumor manifestation, and allows discussion of neuroradiologic findings.

METHODS

Retrospective case series of five patients from three tertiary referral centers (1997 – 2011) and literature review. Three patients from the Zurich University Hospital, Switzerland, one patient from the Goldschleger Eye Institute Tel Aviv, Israel, and one patient from the Egas Moniz Hospital Lisbon, Portugal are reported. All patients underwent biomicroscopy of the fundus and imaging of brain and orbits. In two

patients fluorescein angiography, and in one patient more extensive work-up with an electroretinogram, genetic testing, and temporal artery biopsy was performed. Diagnosis was confirmed by biopsy in all patients. No ethical board approval was required from our institute when the data was collected (2012-2013).

RESULTS

Three men and two women aged 54 to 76 years (mean 66.8 years) with malignant optic glioma were identified. Table 2 summarizes their disease manifestation and disease progression.

Patient 1 presented with left-sided visual loss to hand movement (HM) level for five weeks. On examination, the patient had a left relative afferent pupillary defect (RAPD), a blurred left disc margin, pain on retropulsion, and a junctional scotoma. Fluorescein angiography showed unspecific late leakage of the left disc. These findings suggested a retrobulbar and prechiasmatic lesion. MRI showed involvement of the left optic nerve, optic chiasm, thalamus, mesencephalon and pons with enhancement on T1-weighted images, and hyperintensity on FLAIR and T2 images (Fig. 1). There was progression to disc edema with stasis retinopathy seven weeks later, and to optic atrophy another three months later. The right fundus was normal. Histopathology was obtained from a biopsy via left pterional craniotomy and revealed glioblastoma. The patient received combined temozolomide chemoradiotherapy with irradiation of the involved field (30 x 2 Gy planned, 24 x 2 Gy given), however, died during therapy four and a half months after diagnosis, probably due to tumorous infiltration of the brainstem.

Patient 2 presented with painful eye movements, scintillations, right-sided visual loss (20/30), right RAPD and disc edema. The clinical picture and MRI scan with right optic nerve swelling, enhancement on T1-weighted images and hyperintensity in T2-weighted images were interpreted as optic neuritis. The patient was placed on intravenous methylprednisolone and oral taper twice with resolution of pain, but had progressive visual loss to hand movements (HM) within two months due to a central scotoma in the right eye. The initial MRI scan had revealed a 2 cm lesion with abnormal signal intensity and a 2 mm enhancing spot in the right medial temporal gyrus of unknown etiology. Four months later, follow-up MRI showed progression of the latter. The subsequent cerebral biopsy allowed diagnosis of a multifocal glioblastoma. Despite combined temozolomide chemoradiotherapy with irradiation of the involved field (30 x 1.8 Gy), and bevacizumab salvage therapy, the patient experienced progressive tumor growth with bilateral involvement of the optic nerves, chiasm, tracts, as well as left thalamus und right temporal lobe. After seven months, vision in the left eye started to deteriorate, finally resulting in bilateral optic disc atrophy with no light perception (NLP) of the right eye and faint light perception (LP) of the left eye. The patient died within 18 months of disease onset.

Patient 3 reported painless right-sided visual loss over night. Initial visual acuity of right eye HM and left eye 20/30 further deteriorated to right eye NLP and left eye 20/400 with temporal hemianopia within six weeks. Fundoscopy showed a membranous structure of the right optic disc (Fig. 2a) with progressive vitreous spread over a four months period (Fig. 2b-c). MRI demonstrated a homogeneously enhancing chiasmatic tumor (Fig. 2d) with extension to both optic tracts and optic nerves (right intraorbital and left intracranial portion). The tumor was hyperintense on T2-weighted images, and isointense on native T1 images. Biopsy via right pterional

craniotomy allowed the diagnosis of anaplastic astrocytoma. The tumor progressed despite involved-field radiotherapy (34 x 1.8 Gy). The patient became comatose and died from pneumonia six months after diagnosis. Autopsy finally revealed pleomorphic, astrocytic tumor cells, pseudopalisading necrosis and microvascular proliferation (Fig. 2e-f), consistent with the diagnosis of glioblastoma.

Patient 4 presented with painless unilateral visual blur (right 20/50, left 20/25), impaired color vision and RAPD in the right eye. Both fundi were normal. Automated perimetry revealed superior constriction on the right and an inferior arcuate defect on the left. MRI was read as suspected vague enhancement of the right optic nerve. Lumbar puncture and laboratory work-up for inflammatory or hematological diseases were normal. Intravenous methylprednisolone for five days and oral taper was initiated without effect. Vision deteriorated to NLP in both eyes within six weeks. At that point an electroretinogram was obtained in order to rule out carcinoma associated retinopathy. Genetic testing for Leber hereditary optic neuropathy was negative, temporal artery biopsy ruled out arteritis, and fluorescein angiography was normal. A follow-up MRI three months after onset of symptoms showed bilateral optic nerve enhancement on T1-weighted images, and hyperintensity in T2-weighted images. Optic nerve biopsy via lateral orbitotomy was unrevealing. MRI two months later showed progressive enlargement of the prechiasmatic optic nerves and chiasm suggestive for malignant optic glioma. Biopsy via pterional craniotomy confirmed glioblastoma. Combined temozolomide chemoradiotherapy was recommended. However, the patient decided against temozolomide. The tumor progressed despite involved-field irradiation (28 x 1.8 Gy) and the patient died one year after presentation.

Patient 5 noticed painless visual loss in the right eye for five weeks. Visual acuity was 20/100 with impaired color vision and RAPD in the right eye, and 20/30 with normal color vision in the left eye. Fundoscopy revealed optic disc swelling with hemorrhages and exsudates in the right eye. An arteritic cause could be ruled out, and a diagnosis of atypical NAION was made. Four months later, the patient was referred with progressive deterioration to LP in the right eye and visual loss in the left eye to finger counting level. Fundoscopy revealed shunt vessels and a combined retinal artery and venous occlusion in the right eye, whereas the left fundus was normal. Visual fields were not tested because vision was too low. The MRI was suggestive for malignant optic glioma with bilateral thickening and enhancement of the prechiasmatic optic nerves, chiasm, and tract on T1-weighted images, T1 iso- to hypointensity on native images, and hyperintensity on T2-weighted images (Fig. 3a-c). The diagnosis of glioblastoma was confirmed by right optic nerve biopsy via pterional craniotomy. The patient underwent involved-field radiotherapy, however, died within seven months of symptom onset. Precise information about radiotherapy dose could not be retrieved from the records.

DISCUSSION

Malignant optic glioma of adulthood is a rare, invasive neoplasm of the anterior visual pathway with 66 cases reported. By 2004, Wabbels et al. [4] reviewed 45 cases. Including our five patients, 21 additional cases have been published since (Tables 2 and 3) [5-18]. Mean age of onset of all 66 cases is 57 years (standard deviation ±15; range 22 – 83), with women and men almost equally affected (30 females and 36 males). It rarely occurs in paediatric populations, either as a primary high-grade glioma [19-22] or as malignant transformation of low-grade gliomas [20, 23-25]. Patients suffer from rapidly progressive visual acuity and visual field loss, usually leading to blindness. Depending on tumor localization and extension, visual field defects might be unspecific or show localizing patterns.

With onset of symptoms, all our patients experienced visual loss within one to two months in at least one eye. Patient 2 had a delayed involvement of the fellow eye after seven months. Patient 1 initially seemed to have a strictly unilateral infiltration of the chiasm (Fig. 1) with preserved visual function of the fellow eye. However, there was neuroradiologic evidence of diffuse chiasmatic infiltration and extension to both optic tracts within four months of disease onset, two weeks before the patient passed away. Interestingly, purely unilateral involvement of the anterior visual pathway has been reported in one patient described by Wabbels et al. [4] with a follow-up period of 12 months until death.

At an early stage, clinical findings might suggest anterior ischemic optic neuropathy (patient 5) or inflammatory neuropathy (patient 2 and 4) with minimal neuroradiologic findings and transient responsiveness to steroids. However, progressive visual acuity and visual field deterioration, progressive dyschromatopsia, subsequent retinal vasular occlusions (patient 1), ocular ischemia as well as ocular pain, headaches, ophthalmoplegia, proptosis and other neurological deficits depending on tumor

localization and extension [4] point towards a possible malignant infiltrative disease, and a follow-up MRI should be obtained.

Neuroradiologic findings are unspecific, usually described as contrast enhancement and eventual thickening of the optic nerve, chiasm or tract in T1-weighted images [4, 26], with iso- to hypointensity on native T1 images [27, 28]. T2 *hyper*intensity of the affected anterior visual pathway is a matter of debate [27]. It was first described by Albers et al. [29] in one patient. Friedman et al. [28] presented a second case, and suggested T2 hyperintensity as a possible distinguishing feature of malignant optic glioma versus sarcoidosis with its tendency to *hypo*intensity on T2-weighted images. However, T2 signal intensity is variable in sarcoidosis [30]. Most authors did not comment on neuroradiologic findings of T2-weighted images in malignant optic glioma. In two more recent cases [5, 15] T2 hyperintensity was described, whereas Wabbels et al. [4] explicitly did not find T2 hyperintensity of the optic nerve and chiasm. Our case series supports T2 or FLAIR hyperintensity as a characteristic, albeit unspecific finding of malignant optic glioma, since it was evident in all five patients. This is consistent with neuroradiologic findings in the better characterized cerebral high-grade gliomas [31]. With regard to imaging features, differential diagnosis of a suspected malignant optic glioma still includes demyelinating, infectious, granulomatous, vasculitic and infiltrative optic neuropathies [30]. CT imaging is not helpful in diagnosing malignant optic glioma.

So far, obtaining a biopsy is mandatory for diagnosis, and in case of an unspecific inflammatory histopathologic result, the biopsy might have to be repeated in a patient with a progressive, presumably neoplastic disease as in our patient 4 [13]. Interestingly, patient 3 had documented progression of a grade III glioma (biopsy) to a grade IV glioma (autopsy), which is unique in the current literature on adult

malignant optic glioma. However, it might also simply reflect the tumor heterogeneity with sampling bias.

Considering the aggressively invasive behavior of malignant astrocytomas, intraocular tumor extension is surprisingly rare. While a mechanical barrier at the level of the lamina cribrosa seems plausible, a biological barrier influencing local tumor growth might be suspected as well. Intravitreal seeding of malignant optic glioma of adulthood has not been reported before and makes our case 3 unique. Dumas-Stoeckel et al. [12] presented one patient in the French literature with subretinal tumor extension and combined central retinal vein and artery occlusion. Neither in this latter nor in our patient was intraocular growth confirmed histologically, though.

The standard of care for newly diagnosed high-grade astrocytomas consists of surgery or biopsy as feasible followed by radiotherapy alone (WHO grade III) or temozolomide chemoradiotherapy (WHO grade IV). The introduction of temozolomide increased the median survival of glioblastoma patients by 2-3 months and the likelihood of 2-year survival from 10% to 26% [32]. In contrast, the standard radiotherapy regimen of 54-60 Gy administered in 1.8-2 Gy fractions has remained essentially unaltered over the last decades. Risk structures such as optic nerves, chiasm or brain stem commonly receive no more than 54 Gy. Recurrence or progression may be treated with re-resection, a second course of radiotherapy, or most commonly, using systemic alkylating agent chemotherapy or the VEGF antibody, bevacizumab [33]. The course of disease has not considerably improved over the last century [1], and malignant optic glioma remains lethal within one to two years [4]. The latter also holds true for our patients.

Advances in the understanding of tumor biology have yet failed to translate into effective treatment regimens [34]. However as research evolves, it is our hope that

patients affected from a disease as devastating as malignant optic glioma will benefit from early diagnosis and treatment in the future.

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Legends:

Fig. 1: Coronal T2-weighted images of patient 1 with multifocal glioblastoma show hyperintensity of the left optic nerve (a), left chiasm (b) and infiltration of thalamus, mesencephalon and pons (c). Four months later the tumor diffusely infiltrated the whole chiasm.

Fig. 2 (patient 3): A membranous structure of the right optic disc (a) progressed in size (b) and resulted in vitreous spread (c) over a four months period. The left optic nerve was unremarkable. The axial (d) MRI scan shows impressive thickening of the chiasm with homogeneous contrast enhancement on T1-weighted images. Autopsy revealed diffuse infiltration of the optic nerve and chiasm with pleomorphic, astrocytic tumor cells, with pseudopalisading necrosis (e) and microvascular proliferation (f), the two features distinguishing glioblastoma from anaplastic astrocytoma.

Fig. 3 (patient 5): The coronal MRI scans show bilateral thickening of the optic nerve with hyperintensity in T2-weighted images (a), iso- to hypointensity in native T1-weighted images (b) and bilateral enhancement (c) five months after onset of symptoms.

Table 1: Current WHO classification of CNS astrocytic tumors, modified from Louis et al. (2007) [2]

Table 2: Summary of patient characteristics, disease manifestation and disease progression

Abbreviations: OD right eye, OS left eye, OU both eyes, VL visual loss, AA anaplastic astrocytoma WHO grade III, GBM glioblastoma WHO grade IV, w weeks, mt months, TMZ/RT → TMZ radiotherapy with concomitant and adjuvant temozolomide (according to Stupp et al. 2005) [32], RT radiotherapy, TMZ temozolomide, NAION non-arteritic ischemic optic neuropathy, CAR carcinoma associated retinopathy, CRAO central retinal artery occlusion, CRVO central retinal vein occlusion, ↓ hypointense, → isointense, ↑ hyperintense, +contrast ↑ contrast-enhancing.

Table 3: Summary of 16 published cases since the review of 45 cases by Wabbels et al. (2004) [4]. A case of gemistocytic astrocytoma was included because it had a rather malignant course with survival of 12 months despite multimodality treatment (Simao et al. 2011).

Abbreviations: NK not known, OD right eye, OS left eye, OU both eyes, AA anaplastic astrocytoma WHO grade III, GBM glioblastoma WHO grade IV, w weeks, mt months, chemo chemotherapy (chemotherapeutic agent indicated where available), RT radiotherapy (total dose indicated where available), chemo/RT combined chemoradiotherapy, TMZ temozolomide, PION posterior ischemic optic neuropathy, NAION non-arteritic anterior ischemic optic neuropathy, CRAO central retinal artery occlusion, CRVO central retinal vein occlusion

Malignant optic glioma

Astrocytic tumors	WHO grade I	WHO grade II	WHO grade III	WHO grade IV
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•

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2	M, 54	Yes	Optic neuritis	Disc edema OD → disc atrophy OU	Central scotoma OD	T1+contrast ↑ T2↑	2 mt (OD) 7 mt (OS)	IV, GBM	TMZ/RT → TMZ (30 x 1.8 Gy), Bevacizumab at progression	18 mt	- Multifocal GBM
3	F, 64	No	Tumor	Disc membrane OD → vitreous spread Initially normal OS	VL OD with temporal hemianopia OS	T1→ T1+contrast ↑ T2↑	<1 w (OD) 6 w (OS)	III, AA → IV, GBM	RT (34 x 1.8 Gy)	6 mt	- Intraocular tumor growth - III, AA (biopsy) → IV, GBM (autopsy)
4	M, 75	No	Optic neuritis, CAR	Initially normal OU	OD unspecific OS arcuate scotoma	T1+contrast ↑ T2↑	6 w (OU)	IV, GBM	RT (28 x 1.8 Gy), patient decided against TMZ	12 mt	- Only second biopsy diagnostic
5	F, 76	No	NAION	Disc edema → stasis retinopathy, exsudates → CRAO & CRVO OD Initially normal OS	Not documented.	T1↓→ T1+contrast ↑ T2↑	5 w (OD) 4 mt (OS)	IV, GBM	RT (dose not known)	7 mt	- Retinal vessel occlusion

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Dumas-Stoeckel et al. 2010	M/73	OU	<1 mt OS 4 mt OD	NAION	AA	chemo/RT	~5-6 mt
Matloob et al. 2011	F/63	OU	<1 mt OD ~3-6 mt OS	optic neuritis	GBM	chemo (TMZ)	6 mt
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Kang et al. 2012	F/60	OU	2 mt OU	inflammatory optic neuropathy	AA or GBM (small sample)	TMZ/RT (60 Gy) → TMZ	8 mt
Ashur-Fabian et al. 2013	M/64	OU	~6 mt OS NK OD	NK	GBM	TMZ/RT (60 Gy) → TMZ, propylthiouracil, carboplatin	54 mt
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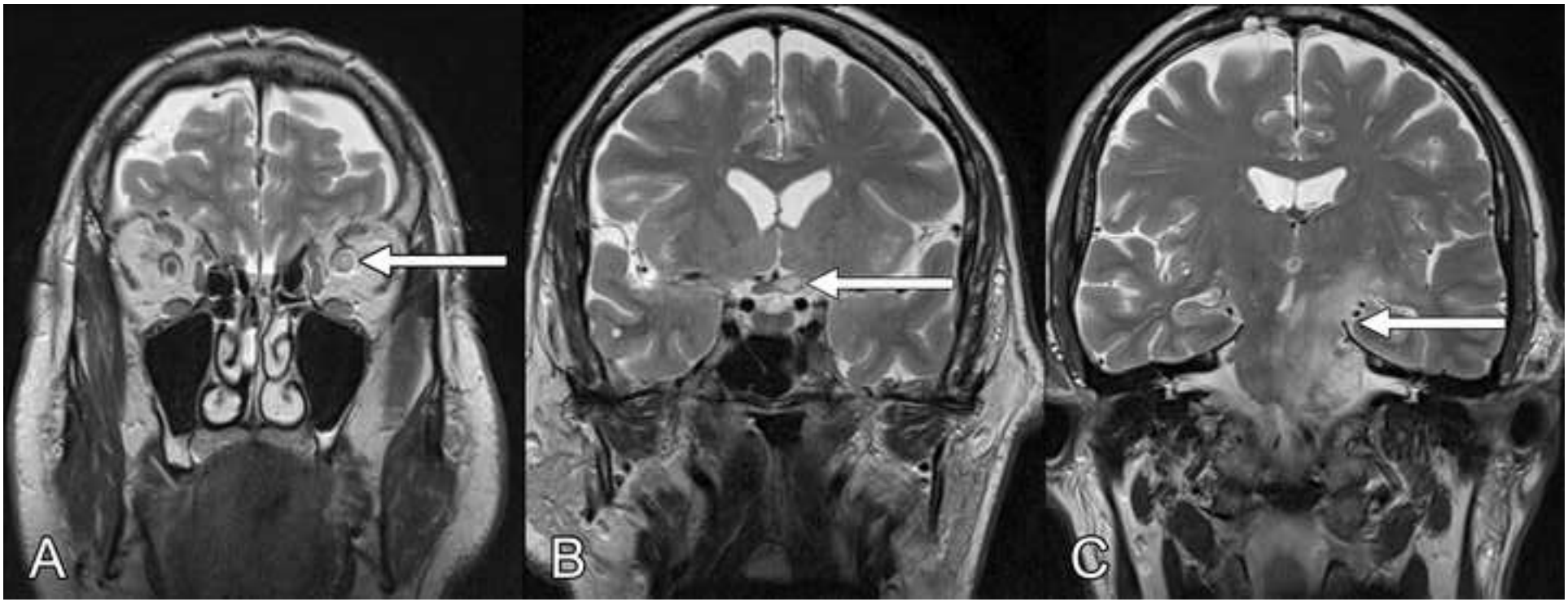

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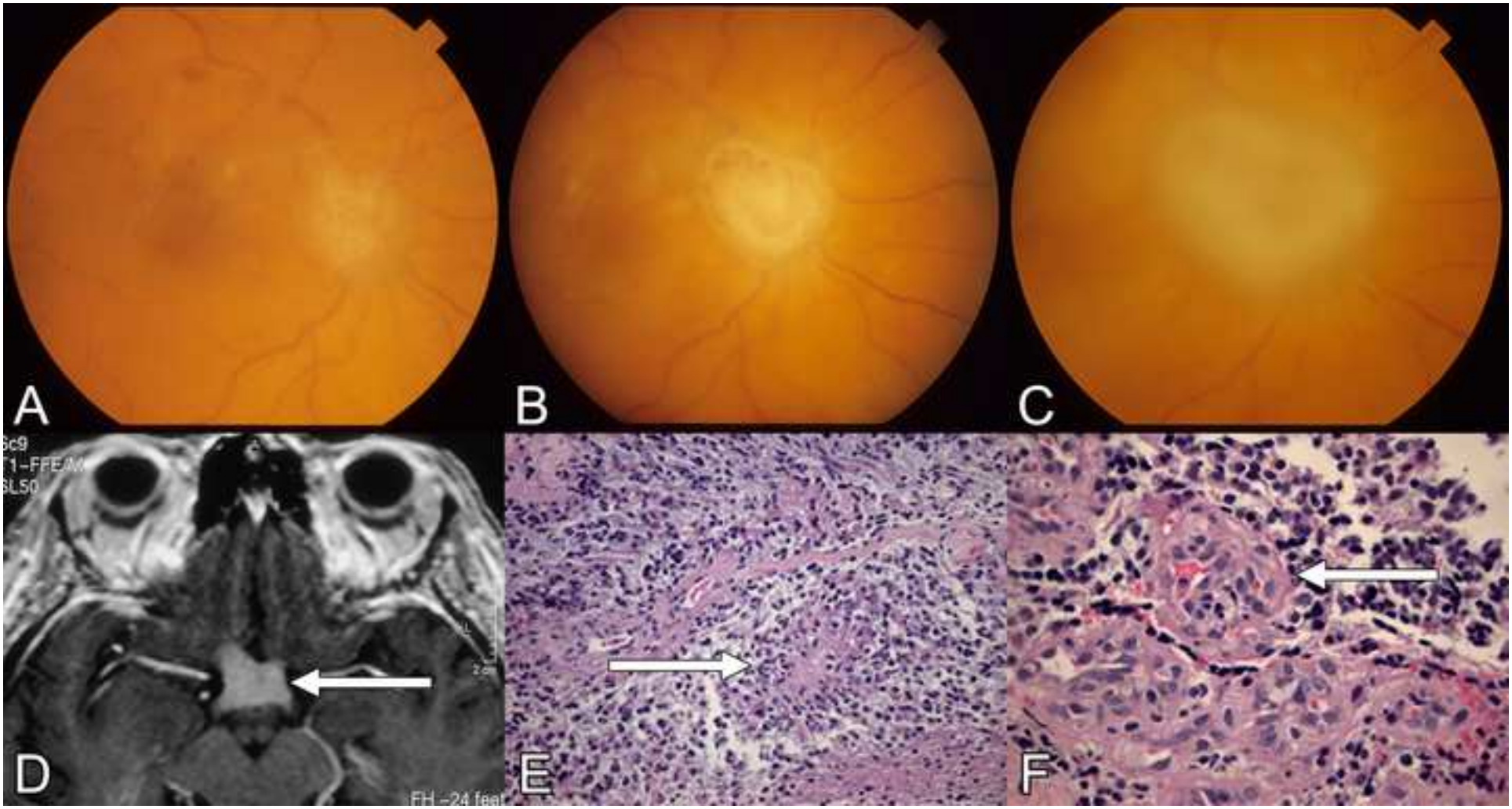

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